



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61F 2/04		A1	(11) International Publication Number: WO 00/18321 (43) International Publication Date: 6 April 2000 (06.04.00)
(21) International Application Number: PCT/US99/20895		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 28 September 1999 (28.09.99)			
(30) Priority Data: 09/161,314 28 September 1998 (28.09.98) US			
(71) Applicant: INTERA TECHNOLOGIES, INC. [US/US]; Bonny Oaks Industrial Park, Building C4301, Founders Way, Chattanooga, TN 37422 (US).			
(72) Inventor: MALLEN, Ted, A.; 121 Rolling Hills Drive, Chattanooga, TN 37343 (US).		Published <i>With international search report.</i>	
(74) Agents: KELLY, Richard, D. et al.; Oblon, Spivak, McClelland, Maier & Neustadt, P.C., Suite 400, 1755 South Jefferson Davis Highway, Arlington, VA 22202 (US).			

(54) Title: HYDROPHILIC SYNTHETIC BLOOD VESSELS

(57) Abstract

The present invention provides hydrophilic synthetic blood vessel, i.e., artificial vascular grafts or prostheses, formed from hydrophilic synthetic polymer fibers. Also provided are medical devices having one or more surfaces comprised of the hydrophilic synthetic polymer fibers.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Hydrophilic Synthetic Blood Vessels

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to hydrophilic synthetic blood vessels, i.e., artificial vascular grafts or prostheses, formed from knitted hydrophilic synthetic polymer fibers. The present invention also relates to methods of making the synthetic blood vessels and to methods of grafting blood vessels using the same. The present invention also relates to implantable medical devices which have at least one surface comprised of the hydrophilic synthetic polymer fibers.

Discussion of the Background

The use of artificial grafts or prostheses to replace and repair portions of human blood vessels that have become damaged due to disease and injury is well known. Numerous attempts have been made to provide a prosthetic device that satisfies the requirements of biocompatibility, durability, and ease of use. These attempts have included implantation of blood vessels derived from donor humans and animals as well as synthetically fabricated prostheses.

Among the synthetic prostheses, knitted or woven fabrics have long been used to form tubular grafts. However, unlike natural blood vessels provided from donors, synthetic grafts must be fabricated in a manner which provides them with properties that sufficiently simulate natural blood vessels. In particular, a vascular prosthesis should be substantially impervious to blood loss even in patients that have been heparinized. This may be achieved by minimizing the permeability of the graft to water and biological fluids. The prosthesis should also have good surgical handling characteristics, have low thrombogenicity, be free from embolic complications, have no adverse affect on blood, have features that encourage fibroblastic ingrowth, and have intrinsic strength characteristics sufficient to maintain dimensional stability even after a prolonged period in vivo. In some cases it is also desirable that such prosthetic grafts remain pliable and preserved in a relatively dry state for extended periods prior to use. This condition enhances the storage life of the graft and thus enhances

its convenience to the surgeon and the hospital. It is very important that materials used for artificial organs in general should not cause any toxic, carcinogenic, pyrogenic or allergic effect nor any adverse sue or skin reaction, etc., in the body. In particular, materials of vascular grafts which are used to replace surgically damaged blood vessels should have flexibility as well as anti-thrombogenic properties and be easy to fabricate. Nylon, polyester, polytetrafluoro ethylene polypropylene, polyacrylonitrile, etc. have been used as materials to fabricate vascular grafts. Among them PTFE and polyester are now widely used since they do not have significant property changes in the body after long term use. Polyester, in particular polyethyleneterephthalate (trade name: Dacron), is most widely used as the material of vascular grafts because it is easy to handle and easy to fabricate.

Materials such as Dacron and Nylon fibers are hydrophobic and therefore have less than ideal compatibility with the surrounding aqueous environment when grafts made from these materials are implanted into patients. Attempts have been made to make these fibers more biocompatible. For example, polyester fibers have been surface-modified with glycoproteins and proteins that interfere with the blood-clotting cascade (see M. Bide, Int. Conf. Exhib., AATCC (1992) 336-42). Polyester fibers have also been impregnated with polysaccharides to increase the adhesion properties of the fibers (see U.S. 5,415,619). However, biomolecules such as proteins, glycoproteins and sugars, etc. have limited stability and may not have the desired durability needed for large-scale production of modified fibers and, especially, stability during storage prior to implantation in patients.

Accordingly, there remains a need for artificial blood vessels that are made from synthetic, man-made fiber materials that have the desired biocompatibility and durability properties.

SUMMARY OF THE INVENTION

The present invention is based on the recognition that hydrophilic synthetic fibers which are used to manufacture textiles may be used to prepare knitted synthetic blood vessels (i.e., synthetic vascular or arterial grafts) which have excellent biocompatibility. Such synthetic blood vessels will be "friendly" to the recipient, e.g., a human. Blood cells and other cells, e.g., endothelial cells, will be able to penetrate and interact with the foreign synthetic blood vessel medium and become well established. Endothelial cells will be able to

line the inventive blood vessels much like natural blood vessels. In addition, clotting may be prevented in the blood vessels, and the vessel will be a good conduit for blood flow. In addition, since these fibers are already used to make textile products, the synthetic blood vessels are expected to have desirable stability and durability properties. The synthetic fibers may also be used in other implantable medical devices.

Accordingly, it is an object of the present invention to provide synthetic blood vessels which provide in one or more, and preferably all, of the following properties: (1) better and faster acceptance of the substrate by the body, (2) quicker and better clotting or sealing the blood vessel from leakage, (3) a better environment for endothelial cell lining formation, (4) a decrease in the incidence of infection, and (5) a decrease in clots forming in the blood supply.

It is another object of the invention to provide artificial implantable medical devices which have the desired biocompatibility properties.

This object, and others, is accomplished with a synthetic blood vessel comprised of hydrophilic synthetic fibers.

The object of the invention are also accomplished with an implantable medical device comprising at least one surface comprised of hydrophilic synthetic fibers.

Various other objects, features and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood from the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The synthetic blood vessel of the present invention is a product which is fabricated from hydrophilic synthetic polymer fibers. The fibers may be knitted, woven, non-woven, etc. For a description of knitted, woven, non-woven fiber products, and other information relating to fibers, see Kirk-Othmer Chemical Encyclopedia of Chemical Technology, Volume 10, Fourth Edition, 1993, pp. 539-744, incorporated herein by reference. The synthetic polymer fiber may be made of a wide variety of polymers, including, polyamides (e.g., nylons), polyesters (e.g., Dacron), polytetrafluoroethylene (PTFE), polypropylene or polyacrylonitrile. Polyamide and polyester fibers are particularly preferred.

The hydrophilic polymer fiber is fabricated into the form of a tube to produce the inventive synthetic blood vessel. Accordingly, the fibers form the wall of the tube and define

a lumen in the center of the tube through which fluid, e.g., blood, can flow. The lumen has openings at each end of the tube. The length of the tube may vary over a wide range. Preferably, the tube has a length of from 1 mm to 1 m, inclusive of all specific values and subranges therebetween, e.g., 2, 5, 10, 20, 50, 100, 250, 500 and 750 mm. The outer diameter of the tube may also vary widely. Preferably, the outer diameter is 2 to 30 mm, inclusive of all specific values and subranges therebetween, e.g., 2, 5, 10, 15, 20 and 25 mm. The internal diameter of the lumen may vary from 1 to 29 mm, inclusive of all values and subranges therebetween, e.g., 2, 5, 10, 15, 20 and 25 mm. The outer and inner diameters may vary with the type of vascular graft. For example, arterial prostheses will generally have an outer diameter from 4 to 20 mm, inclusive of all values and subranges therebetween, whereas venous prostheses will have an outer diameter of 6 to 28 mm, inclusive of all values and subranges therebetween. The synthetic blood vessel is preferably in the form of an elongate tube, i.e., the length of the tube is greater than the width of the tube. The synthetic blood vessels may be used as artificial arteries, veins or capillaries.

The fibers may also be used in variety of other implantable medical devices in addition to the synthetic blood vessels described above. Such devices contain one or more surfaces composed of the hydrophilic synthetic fibers. The surface(s) comprised of the fibers are designed to be in contact with biological fluids, e.g., blood, urine, etc. Examples of other implantable medical devices include artificial kidneys, catheters, pacemakers, artificial hearts, artificial bones, artificial joints, etc. For a discussion of prosthetic and biomedical devices see Kirk-Othmer Chemical Encyclopedia of Chemical Technology, Volume 20, Fourth Edition, 1993, pp. 351-395, incorporated herein by reference.

The fibers are preferably of the size used to make athletic weight socks, e.g., having a fiber denier or equivalent thickness unit of about 0.5-3500 denier, preferably 50-200 denier. The hydrophilic fibers, preferably spun or continuous filament, can be made into the inventive synthetic blood vessel using conventional techniques and equipment and no modification of the techniques is required.

To obtain the beneficial effects of the present invention, it is important to use hydrophilic synthetic fibers. These fibers may be made from fibers which are otherwise hydrophobic by rendering them hydrophilic via a hydrophilizing treatment.

Many techniques have been suggested for rendering fabrics hydrophilic. Some

techniques involve modifying the surface of the fabric to introduce small voids so as to physically trap the aqueous media into the fabric. Other techniques involving chemically modifying the surface of the fabric have been suggested in the patent literature, see for example U.S. Pat. Nos. 3,652,212, 4,242,408, 4,448,839, 4,808,188, 4,081,381 incorporated herein by reference. A polyester fabric under the trade name VISA exhibiting the necessary hydrophilic properties is sold by Milliken & Co., and fabric under the trade name SCOTCH RELEASE is sold by manufacturers using 3M chemicals. Other fibers having hydrophilic properties which may be used in the invention include AKWATEK and AKWADYNE sold by Comfort Technologies, Inc., in which the fibers are treated with lithium cations and borohydride anions. Further, hydrophobic synthetic fibers may be treated with topical hydrophilic wetting agents.

Another example of suitable fibers are polymers having bonded thereto a hydrophilic copolymer which comprises the reaction product of a primary hydroxylate and a silane as described in U.S. Pat. No. 5,408,012, incorporated herein by reference for a more complete description of preparing these hydrophilic fiber materials.

MILASE T fibers may also be used to prepare the inventive synthetic blood vessel. These fibers are composed of random ethylene terephthalate/polyethylene glycol (PEG) terephthalate units.

The surface of the hydrophilic fibers may be treated by any suitable molecular, physical or chemical process or combination thereof, to render the fibers hydrophilic. For example, fibers caustically etched with grooves are hydrophilic and transport moisture, and are known in this art. Additionally, fibers having a modified cross-section, i.e., irregular, non-oval, fluted or grooved fibers are known hydrophilic fibers and may be used to prepare the synthetic blood vessel of the present invention. Copolymer fibers prepared by combining the extrusion of synthetic fibers and fibers containing absorbing components such as poly(ethylene glycol) are acceptable for use in the present invention. Examples of the fibers described above are commercially available under the tradenames COOLMAX by DuPont (non-oval fiber) and HYDROPHIL by Allied (copolymer extrusion with poly (ethylene glycol) fibers). COOLMAX fibers have a relatively large surface area in relation to volume. In addition, these fibers have four channels along their respective longitudinal dimensions to encourage the wicking of fluids. Hollow synthetic fibers may be hydrophilic and are capable

of transporting water through the capillary fibers. Such hollow fibers are known and available commercially, for example, THERMAX fibers available from DuPont.

Hydrophobic fibers, such as nylon and polyester, which have been rendered hydrophilic by chemical surface treatment are particularly preferred for manufacturing the synthetic blood vessel of the present invention. Suitable chemical processes are described, for example, in U.S. Pat. No. 4,705,831; U.S. Pat. No. 4,726,968; U.S. Pat. No. 4,743,267; U.S. Pat. No. 4,672,005; U.S. Pat. No. 4,563,507; U.S. Pat. No. 4,806,125; U.S. Pat. No. 5,154,727; and U.S. Patent Application 08/710,715, filed September 20, 1996 (Attorney Docket No. 1876-0106-40). These patents and patent application are incorporated herein by reference for a more complete description of suitable chemical modification processes and synthetic hydrophilic fabrics which are prepared using these processes. This type of hydrophilic fiber is commercially available under the tradename INTERA from Intera Corporation. Treatment of the hydrophobic fibers to chemically modify the surface thereof has the additional advantage of minimizing or preventing the treated fibers from unraveling when fabricated into the synthetic blood vessel.

In a particularly preferred process, the hydrophobic synthetic polymer fiber substrate is contacted with an aqueous mixture containing a water-soluble vinyl monomer and a hydrophobic vinyl monomer at a temperature of between about 40°-100°C. Polymerization of the water-soluble monomer is then initiated by a chemical or physical initiator to form a vinyl polymer evenly disposed on the substrate fiber. Suitable water-soluble vinyl monomers and hydrophobic monomers are described in U.S. Pat. No. 4,672,005.

As discussed above, the fibers used to prepare the inventive blood vessels are suitable for the manufacture of textiles, and are preferably completely synthetic. This refers to fibers that are composed entirely of man-made materials, and not materials which occur in or are isolated from humans. Accordingly, in this embodiment, excluded are substrate fibers which have been modified with biomolecules, such as amino acids, peptides, polypeptides, proteins, glycopeptides, glycoproteins and sugars (e.g., oligosaccharides (and derivatives thereof) or sugar monomers).

The hydrophilic synthetic fibers used to prepare the inventive synthetic blood vessel should effectively transport blood. Preferably, the hydrophilic fiber should wick water at a rate of at least 1/10 inch per initial min., more preferably at least 1/2 inch per initial min., in a

standard wicking test, for example the standard TDI No. 4 (Textile Distributors Institute) test. Alternatively, the fabric should wick whole human blood in the vertical absorption test described below at least 0.25 inches in 30 seconds, preferably at least 0.75 inches, more preferably at least 1 inch and most preferably at least 1.2 inches, in 30 seconds.

Alternatively, the fabric should have a drop time in the drop test described below of at most 220 seconds, preferably at most 100 seconds, more preferably at most 50 seconds, and, most preferably, at most ten seconds. The fabric may have even lower drop times, such as at most 5, 3, 2 or 1 second. Hydrophilic fabrics suitable for use in the present invention can be readily determined by one having ordinary skill in this art.

Vertical wicking of hydrophilic fibers which maybe used in the present invention can be determined by the following procedures. A piece of fabric measuring 1x6 inches made from the fibers is prepared. A non-indelible ink line is drawn vertically through the middle of the fabrics such that the path of transported water is more visible. The fabric is held vertically and immersed to a depth of 1/2 inch in a 200 milliliter beaker containing 150 milliliters of water. After 30 seconds of elapsed time, the vertical distance traveled by the transported water is measured.

The inventive synthetic blood vessel may be used to graft blood vessels according to procedures which are routine and well-known to those of ordinary skill in this art. Briefly, blood vessels (e.g., arteries, veins or capillaries) by contacting a first blood vessel with one end of the synthetic blood vessel and contacting a second blood vessel with the other end of the synthetic blood vessel, thereby grafting the first and second blood vessels.

Having now fully described the invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

EXAMPLES

Fabrics prepared from several synthetic fibers were used to evaluate the hydrophilicity of the fibers, i.e., affinity for whole human blood. The tests used to demonstrate differential affinity for whole human blood were:

1. Vertical Absorption Test

This test measures the hydrophilicity, i.e., power or attraction of the substrate for blood, by how far the fabric pulls the blood out of a vial in a given period of time: 30 seconds. This test is performed by vertically placing a rectangular strip of the fabric (approximately $\frac{1}{2}$ inch wide, 6 inches long, and $\frac{1}{16}$ inch thick) at its tip in a vial of blood and recording against time (30 seconds) the height to which the blood rises in the fabric.

2. Drop Test

This test measures the hydrophilicity, i.e., power or attraction of the substrate for blood, by how quickly it causes the reflection from the blood drop to disappear. This test is performed by dropping a drop of blood from a dropper from a height of $\frac{1}{2}$ " onto a 3" x 3" horizontally laid square of the fabric and recording the time for the drop to be absorbed such that there is no reflection from the drop of blood.

TEST RESULTS
USING WHOLE HUMAN BLOOD
(Temp 72°F; Relative Humidity 60%)

FABRIC	VERTICAL ABSORPTION IN INCHES AFTER 30 SECONDS	DROP TIME IN SECONDS
--------	--	-------------------------

POLYESTERS

1. INTERA POLYESTER	1 1/4 inches	1 second
2. COOLMAX POLYESTER	1 1/8 inches	1 second
3. AKWATEK POLYESTER	3/4 inch	1 second
4. MILEASE T POLYESTER	1 inch	1 second
5. ORDINARY POLYESTER	1/32 inch	>240 seconds (test stopped)

NYLONS

1. INTERA NYLON	1 9/16 inch	1 second
2. ORDINARY NYLON	3/16 inch	>240 seconds (test stopped)

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

Claims

1. A synthetic blood vessel comprised of hydrophilic synthetic fibers.
2. The synthetic blood vessel of Claim 1, where in the fibers are knitted, woven or non-woven.
3. The synthetic blood vessel of Claim 1, where in the fibers are knitted.
4. The synthetic blood vessel of Claim 1, which consists essentially of the hydrophilic synthetic fibers.
5. The synthetic blood vessel of Claim 1, which has a length of 1 mm to 1 m and a diameter of 1 to 30 mm.
6. The synthetic blood vessel of Claim 1, wherein the fibers are hydrophilic polyester or polyamide fibers.
7. The synthetic blood vessel of Claim 1, wherein the fibers have an irregular, non-oval or fluted cross-section.
8. The synthetic blood vessel of Claim 1, wherein the fibers have channels along their respective longitudinal dimensions.
9. The synthetic blood vessel of Claim 1, wherein the fibers are a polyester composed of random ethylene terephthalate/polyethylene glycol (PEG) terephthalate units.
10. The synthetic blood vessel of Claim 1, wherein the fibers are composed of a synthetic polymer having bonded thereto a hydrophilic copolymer which comprises the reaction product of a primary hydroxylate and a silane.

11. The synthetic blood vessel of Claim 1, wherein the fibers are the reaction product obtained by treating a substrate fiber with an aqueous mixture containing a water-soluble vinyl monomer and a hydrophobic vinyl monomer at a temperature of between about 40°-100°C and the initiating polymerization of the water-soluble monomer with a chemical or physical initiator to form a vinyl polymer evenly disposed on the substrate fiber.
12. The synthetic blood vessel of Claim 1, wherein the fibers are hollow.
13. The synthetic blood vessel of Claim 1, which is an artificial artery, vein or capillary.
14. The synthetic blood vessel of Claim 1, which is an artificial artery.
15. A method of making the synthetic blood vessel of Claim 1, comprising knitting the hydrophilic synthetic fibers to form the synthetic blood vessel.
16. A method of grafting blood vessels, comprising contacting a first blood vessel with one end of the synthetic blood vessel of Claim 1 and contacting a second blood vessel with the other end of the synthetic blood vessel, thereby grafting the first and second blood vessels.
17. An implantable medical device comprising at least one surface comprised of hydrophilic synthetic fibers.
18. The implantable medical device of Claim 17, wherein the surface consists essentially of the hydrophilic synthetic fibers.
19. The implantable medical device of Claim 17, wherein the fibers are hydrophilic polyester or polyamide fibers.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/20895

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61F 2/04

US CL :623/1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 606/194; 623/1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	US 5,415,619 A (LEE et al.) 16 May 1995, entire document.	1, 2, 5, 6, 13, 14, 16-19
Y		3, 4, 7-12, 15

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same parent family

Date of the actual completion of the international search
29 NOVEMBER 1999Date of mailing of the international search report
19 JAN 2000Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230Authorized officer
BRUCE SNOW
Telephone No. (703) 308-3255